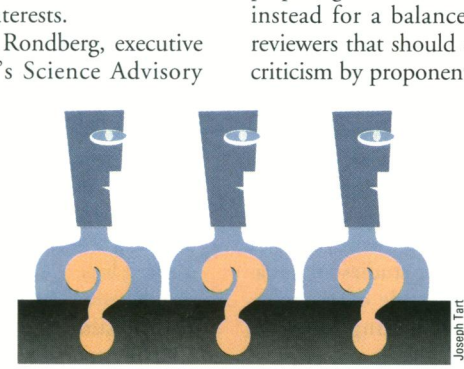
Dioxin Review Blues

The document itself was more than three years in the making, and it looks as if finding a review panel for the EPA's reassessment of dioxin could also become a marathon process. Efforts to appoint a balanced panel are being stymied by the recusals of panel members concerned about potential conflicts of interests.

According to Sam Rondberg, executive secretary of the EPA's Science Advisory Board (SAB), which is responsible for filling the two committees—exposure and environmental health effects—that will review the dioxin reassessment, the problem is finding scientists to fill the growing number of vacancies on the environmental health effects committee left by members who have recused themselves from the review. Said Rondberg, "These people have taken very public positions on [dioxin] and they feel it would be improper for them to review the document." For example, Frederica Perera, the chair of the standing environmental health effects committee, has declined to participate because she sits on the board of the Natural Resources Defense Council which has legal actions pending against the EPA concerning dioxin. Although there is no a legal conflict of interest, Perera stated in her letter of recusal that she wished to avoid such a perception. Said Perera, "This is particularly important in light of the difficulty previous committees have encountered in achieving consensus on the health risks of dioxin."



Joseph Tart

Mystery member. EPA's committee on environmental health effects of dioxin is looking for a few good men and women.

Apparently many others share Perera's sentiments. Committee members Richard Monson of the Harvard School of Public Health, Donald Mattison of the University of Pittsburgh, and Michael Gallo of the Robert Wood Johnson Medical School in New Jersey have all declined to participate because of their public stands on dioxin. Ironically, Gallo and Mattison have gone so far as to sign a letter, along with many other leading dioxin researchers from outside government, criticizing the lack of outside scientists in the development of the risk characterization portion of the reassessment and calling for "careful scrutiny by the scientific community" of these conclusions. Commenting on the letter, Rondberg said that these scientists clearly want a careful review of the risk assessment, "they just don't want to be the ones doing it for the agency."

An impartial panel may be all but impossible, given that most of the country's dioxin experts were involved in some way in producing the eight "State of the Science" chapters of the reassessment. In fact, some committee members, including George Lucier, the federal liaison consultant to the committee, have declined to participate on the basis of their active involvement in preparing the document. The SAB is aiming instead for a balance of positions among reviewers that should deflect some potential criticism by proponents on both sides of the dioxin debate.

According to Rondberg, a factor that may help establish the credibility of the committee's review is a clear and specific charge. Unfortunately, until a committee chair is recruited, completion of the draft charge will be delayed. Rondberg said, however, that the committee is considering 10–12 major issues for the review panel to consider, including toxic equivalency factors and the question of mass balance in terms of exposure.

Rondberg said the SAB is hoping to have a public meeting in March at which the exposure and environmental health effects committees will meet to review the reassessment. After this meeting, a report will be prepared and circulated for comment, and, after being finalized, it will be sent to the EPA administrator.

Mismatch Mania

Scientists are excited about recent studies on mismatch repair. No, it's not a new method for regrouping stray socks from the dryer. Mismatch repair is one of the two major types of DNA repair pathways. Researchers are studying mismatch repair for clues about how this process operates and about the consequences of repair pathway breakdown.

During mismatch repair, errors that occur while DNA is being replicated, including mismatched nucleotides, are fixed. Mismatch repair occurs in species from bacteria to humans. In fact, scientists have found that the proteins encoded by mismatch repair genes are similar throughout the evolutionary chain. Recognition of this similarity and subsequent research on the bacteria *Escherichia coli* led to the discovery that mutations in the DNA repair genes of humans can cause hereditary nonpolyposis colon cancer (HNPCC), one of the most common hereditary cancers. HNPCC may account for as many as 15% of the 20,000 cases of colon cancer in the United States every year.

Recently, Thomas Kunkel and colleagues at the NIEHS found evidence that, although mismatch repair systems among species may be similar, humans may have a far more advanced repair pathway. Kunkel's group looked specifically at a phenomenon called microsatellite instability. Microsatellite DNA is made up of short sequences of nucleotide bases repeated throughout a person's genome. These sequences may vary in length from person to person, but they should be the same within one individual. In HNPCC tumors, however, microsatellite DNA varies in length within the same person. Errors may occur during replication of DNA when the two strands of DNA fail to line up directly, resulting in a new strand that is longer or shorter than the old one and a new double-stranded molecule with a small loop of unpaired DNA. Because microsatellite instability is one of the defects mismatch repair is supposed to correct, researchers believe mutations in mismatch repair genes may be responsible for this alteration in genes, eventually leading to tumor formation.

In *E. coli*, researchers have found that mismatch repair cannot correct microsatellite defects of more than four consecutive unpaired bases. In humans, microsatellite DNA may result in far more than four unpaired DNA loops. Kunkel's group was interested in seeing whether human mismatch repair genes can repair DNA containing more than four unpaired nucleotides. Kunkel found that in at least one colorectal carcinoma cell line, extracts repaired DNA containing loops of 5, 8, or 16 unpaired bases, although the same extracts did not correct loops of four or less unpaired bases, suggesting that humans may have a far more evolved system for repairing DNA than other species. Researcher Richard Fishel of the University of Vermont in Burlington said in a November 4 article in *Science* that evolution of such a repair system "makes a lot of sense from an organism's standpoint. Since the bacterial genome has very few of these [larger loop] repeats, the bacterial enzyme doesn't have to recognize these errors." According to Kunkel, mutant cell lines that are defective in some but not all forms of loop repair probably exist, since quantitative and qualitative differences in stability of microsatellite alleles are found in a variety of tumor cell lines. Further identification of specific alleles of mismatch repair genes might prove useful in future studies of individual tumor susceptibility.